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Impact of high post-loading platelet aggregation on 30-day clinical outcomes after primary percutaneous coronary intervention. The antiplatelet regimen tailoring after primary PCI (ART-PCI) trial

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ABSTRACT

Background: Patients with high post-loading platelet aggregation (PPA) are at increased risk of stent thrombosis and death after primary percutaneous coronary intervention (pPCI). The objective of the present trial was to examine whether high PPA is associated with adverse clinical outcomes in pPCI patients whose therapy was modified in accordance with PPA.

Methods: We analyzed 961 consecutive pPCI patients who underwent pPCI between February 2008 and June 2011. High PPA was defined as PPA > 50%, 24 h after the loading dose. Patients with high PPA were treated with aspirin 300 mg, clopidogrel 150 mg or ticlopidine 500 mg for 30 days. The co-primary efficacy and safety end points at 30 days were major adverse cardiovascular events (MACE) and major bleeding.

Results: We detected high PPA to clopidogrel and aspirin in 44.4% and 16.5% of patients, respectively. The rates of 30-day MACE (adjusted OR 1.76, 95% CI 1.05–2.97), definite subacute stent thrombosis (DSST, adjusted OR 2.15, 95% CI 1.09–4.22) and nonfatal infarction (adjusted OR 3.99, 95% CI 1.57–10.13) were higher in patients with high PPA to clopidogrel compared with responders. High PPA to aspirin was not associated with an adverse 30-day clinical outcome. Compared with high PPA patients who were not tailored, a significantly better outcome with respect to the primary end point was observed in the tailored group (OR 0.42, 95% CI 0.19–0.93).

Conclusion: High PPA to clopidogrel was an independent predictor of 30-day adverse events after pPCI. Among high PPA patients, tailoring was associated with an improved primary outcome.

1. Introduction

Sustained enhancement of post-treatment platelet aggregation was documented after coronary stenting in patients with acute myocardial infarction [1]. Accordingly, adequate platelet inhibition with dual antiplatelet therapy is a key therapeutic goal after primary percutaneous coronary intervention (pPCI), aimed at protecting against stent thrombosis and increased mortality [2]. However, recent studies have shown that up to one third of acute coronary syndrome patients who received clopidogrel loading and up to one seventh of patients who received aspirin loading have high post-loading platelet aggregation (PPA) [3].

Many studies have suggested a relation between a high PPA and increased rate of ischemic events including stent thrombosis in patients with acute coronary syndrome [4–10]. In addition, there is an evidence that 150 mg clopidogrel maintenance dose, compared to conventional daily dose of 75 mg, might improve the effectiveness of platelet inhibition without an increase in the risk of bleeding [11,12]. However, no benefit with respect to the cardiovascular outcomes was documented in acute coronary syndrome patients [13–15]. This study aimed at investigating the impact of high PPA on clinical outcomes in pPCI patients whose antiplatelet regimen was modified in accordance with PPA.

2. Methods

We analyzed 961 consecutive patients with ST elevation myocardial infarction enrolled in the ART-PCI trial (trial registration number: ISRCTN64082539 — http://www.controlled trials.com/ISRCTN64082539) between February 2008, and June 2011. The research protocol was approved by the Ethics Committee of the Clinical Center of Serbia. All participants gave their informed consent in writing.

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2.1. Multiple electrode platelet aggregometry

Multiple electrode aggregometry has been performed using the impedance aggregometer (Multiplate analyzer, Dynabyte GmbH, Munich, Germany). Whole blood was sampled 24 h after the loading dose. In patients who received IIb/IIIa inhibitor tirofiban blood samples were obtained at least 24 h after the completion of tirofiban infusion. ASPI and ADP tests were used to analyze the effect of aspirin and clopidogrel on PRA. Aggregation was continuously recorded for 6 min after arachidonic acid (final concentration 0.5 mM/L) or adenosine-diphosphate (final concentration 6.4 μM/L) were added. Prostaglandin E1 (final concentration 9.4 nM/L) was simultaneously added to increase test's sensitivity to ADP. TRAP test reflects a direct activation of the thrombin receptor using the thrombin receptor activating peptide (final concentration 32 μM/L). Pre- and post PCI analyses of TRAP test were similar reflecting the low sensitivity of the test to aspirin and clopidogrel [16]. PRA above 50%, compared to the basal value estimated by TRAP test, was linked with LR-ness. The same cut-off was used by Bliden et al. [6]. Inclusion and exclusion criteria for tailoring are shown in Table 1. The flow of patients included in the ART-PCI trial is shown on Fig. 1.

2.2. End points and definitions

The ART-PCI specified co-primary end points were: major adverse cardiovascular events (MACE) as an efficiency composite end point, and TIMI major bleeding as a key safety end point. MACE comprised death, nonfatal infarction, ischemia-driven target vessel revascularization and ischemic stroke. Our secondary end points were definite subacute stent thrombosis (DSST) and individual components of MACE. Nonfatal infarction was defined as the presence of: (a) recurrent ischemic chest pain longer than 20 min; (b) ST deviation >0.1 mV or new pathognomonic Q waves (0.04 s or longer) in at least two contiguous electrocardiographic leads, and (c) increase of cardiac troponin above the upper reference limit. Stroke, classified as ischemic or hemorrhagic by computed tomography, was defined as a new onset of focal or global neurological deficit lasting over 24 h. DSST was defined according to the Academic Research Consortium definition as an angiographic or autopsy confirmation of thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent with presence of the acute coronary syndrome within a 48 h time window [17]. Subacute stent thrombosis was defined in a time frame from 24 h to 30 days after stent implantation. Bleeding events were classified according to Thrombolysis In Myocardial Infarction (TIMI) criteria.

Patients were followed-up for adherence to antiplatelet therapy and adverse events at 30 days after enrollment by scheduled telephone interviews and/or outpatient visits. Interviewers were blinded to the results of platelet aggregation. An independent Clinical Event Committee adjudicated the occurrence of major events and major bleeding.

Table 1
Inclusion and exclusion criteria for antiplatelet regimen tailoring.

Inclusion criteria	Exclusion criteria
– 18 years and older	*Pre–procedural*
– Willing consent	– Any history of hemorrhagic stroke
– Alive 24 h after 600 mg clopidogrel loading	– Ischemic stroke within 30 days of randomization
– Ability to comply with study protocol	– Symptomatic peptic ulcer
– Low responder to clopidogrel 600 mg loading dose	– Evidence of active abnormal bleeding within 3 months of randomization
– Low responder to aspirin 300 mg loading dose	– History of recent gastrointestinal bleeding
	– Current therapy with coumadin anticoagulation
	– Pregnancy or nursing
	– Current enrollment in another investigational drug or device study
	Procedural
	– Balloon angioplasty without stent placement
	– Unsuccessful pPCI (post-procedural TIMI flow 0)
	Post-procedural
	– Older than 80 years
	– Active internal bleeding
	– Hemoglobin <10 g/dL or drop in hemoglobin by ≥3 g/dL
	– Platelet count $<100\,000\times10^{-9}$/L.
	– Low basal TRAP value (<500 AU)
	– Indication for permanent anticoagulant therapy
	– Need for urgent surgical revascularization

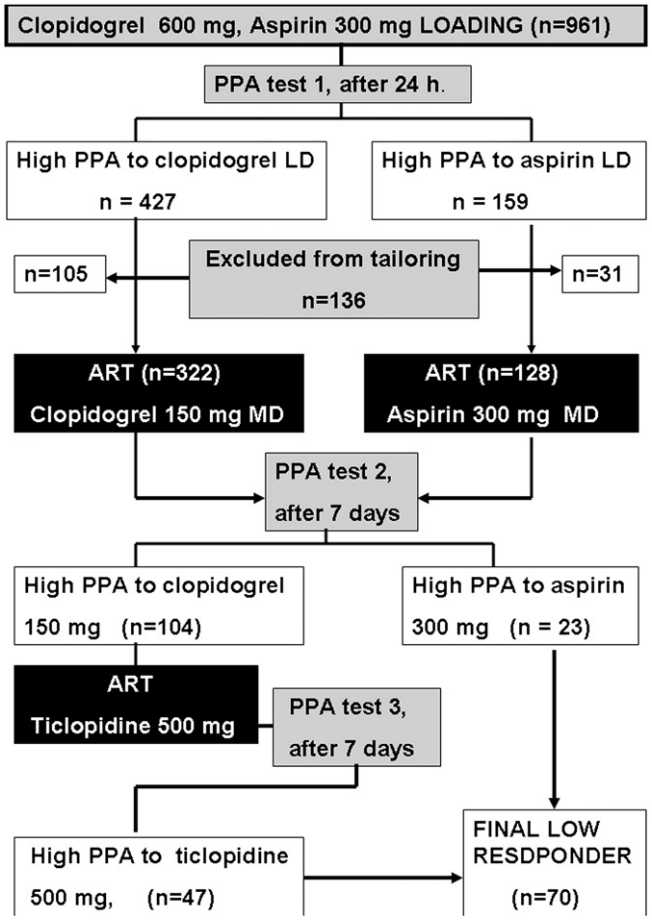

Fig. 1. Patients flow in the ART-PCI trial. PPA = post-treatment platelet aggregation, ART = antiplatelet regimen tailoring, LD = loading dose, MD = maintenance dose.

2.3. Sample size

Assuming the number of LRs to clopidogrel of 33% (2:1 ratio of responders to LRs) and 0.1 versus 0.05 proportion of predicted 30-day MACE, respectively, the sample size of 934 patients provided 80% power to detect the superiority relative to the primary end point at a 2-sided significance level of 0.05. Assuming the number of LRs to aspirin of 15% (6.5:1 ratio of responders to LRs) and 0.12 versus 0.05 proportion of predicted 30-day MACE, respectively, the sample size of 931 patients provided 80% power to detect the superiority relative to the primary end point at a 2-sided significance level of 0.05.

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD or median values with 25th and 75th quartiles, whereas categorical variables were expressed as frequency and percentages. Analysis for normality of data was performed using the Kolmogorov–Smirnov test. Baseline differences between groups were analyzed using Student *t*-test or Mann–Whitney test for continuous variables, and Chi-square test for categorical variables. Data for patients who died before the end of the follow-up were censored at the time of death. Univariable logistic regression model was used to identify baseline differences between groups. Multivariable logistic regression was performed to determine the influence of high PPA on outcomes. Adjustment for differences in baseline characteristics and variables that are known to influence platelet reactivity was performed using propensity score for high PPA, calculated from the multivariable logistic regression. The SPSS statistical software version 18.2 was used (SPSS Inc, Chicago, IL). Two-sided p value <0.05 was considered significant for all analyses.

3. Results

Baseline characteristics of patients in accordance to the response to loading doses of clopidogrel and aspirin are shown in Table 1.

High PPA to clopidogrel loading was detected in 427/961 (44.4%) patients, 159 (16.5%) patients had high PPA to aspirin loading, and 110 (11.4%) patients showed high PPA to aspirin and clopidogrel.